DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 12, 2008 has been entered.

Claim Rejections 35 U.S.C. 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 3, 5-8, 10, 12, 14, 18-26, 83, 84, 87-91, 93, 94, 96-100, 102-105, 108, 109, 112-116 are rejected under 35 U.S.C. 102(b) as being anticipated by Karan et al. (IDS).

4. Karen et al. teaches a lecithin-coated microcrystalline dantrolene composition suitable for intravenous injection. The dried composition may be reconstituted in water at 10-15% (wt/vol. Dantrolene) to form a stable suspension with particle size of 300-800 nm (sodium dantrolene) and 440±150 nm (dantrolene). See, particularly, page 797, the left column. The composition was used as intravenous injection in swines, rats, and dogs. See, particularly, pages 797-798. Karan et al. also teaches that the diameters of the microcrystals are vital as to the pulmonary hypertensive response. See, particularly, page 801, the left column. As to the limitation "water soluble surfactant", note lecithin is an old and well known surfactant. Further, since the application lacks any definition of "water soluble", and lecithin has certain solubility in water, interpretated

broadly, the "water soluble surfactant would read on lecithin." as to safe for intravenous injection, it is noted that the specification defined the safe as:

5. [0015] "Safe for injection". We define "safe for injection" to mean a formulation that can be reliably injected intravenously into appropriate test subjects or model mammals, at relevant clinical doses, with a low incidence of life-threatening complications due to the formulation, where low incidence means less than about 10% of cases, and preferably less than about 1% of cases. In particular, formulation-related toxicities, such as pulmonary emboli (PE) due to supermicron-sized particles or aggregates, pathologically altered arterial pressures, or severe vascular damage, must be limited to low incidence. See page 3.

6. It is note that Karan references discloses incident of pulmonary hypertensive response (page 801), however, it is no way a *life-threatening complication*. Therefore, the composition disclosed by Karan reference would meet the limitation of safe for intravenous rejection.

7.

Claim Rejections 35 U.S.C. 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3, 5-10, 12-14, 18-26, 83-91, 93, 94, 96-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. (IDS), in view of Patel et al. (6,294,192), Ramstack et al. (US 6,495,164), Bosch et al. (US 5,510,118), and Karen et al. (IDS).

3. Ellis teaches dantrolene sodium is an old and well known therapeutical agent, and is known to be administered by any conventional method. The dosage amount is known to be in the

range of up to 139 mg/kg of body weight per day. See, particularly, col. 1, lines 10-66, col. 4, lines 1-5.

4. Ellis et al. do not teach expressly the particular composition in high concentration, or be capable of being formulated to a composition in high concentration, or the particular pharmaceutical acceptable carrier and excipients.

5. However, Patel et al. teaches a pharmaceutical composition and method for delivery of hydrophobic therapeutical agents, such as dantrolene sodium, the composition comprise the therapeutical agent, solubilizer, and surfactants, wherein the solubilizer may be alcohols, such as ethylene glycol, propylene glycol, glycerol, polyethylene glycol (PEG 200-600); amide, such as dimethylacetamide, or mixture thereof. The amount of solubilizer is not particularly limited. The composition may be in the form of solution (diluted preconcentrate), semi-solid dispersion, or multiphase dispersion. The composition may be formulated into various forms suitable for conventional delivery, including oral, topical, transdermal, ocular, parenteral, etc. See, particularly, the abstract, column 24, line 31, col. 25 line 15 to col. 28, line 24, and the claims. For multi-phase dispersion, the solid phase may be in milled, micronized forms. See, particularly, col. 27, lines 11-42. Patel further disclosed that, for dispersion, the particle size is typically less than 20 nm. See, col. 28, line 44 to col. 29, line 4. Ramstack et al. teaches an improved injectable suspension with a concentration of more than 30 mg/ml, wherein the composition is characterized by containing surfactants. See, particularly, the abstract and the claims. Bosch et al. teaches a suspension composition suitable for parenteral administration, comprising water-insoluble nanoparticle therapeutical agent, wherein the average particle sized is about 400 nm and a surface modifier. Suitable surface modifiers include benzalkonium

chloride. See, particularly, the abstract, and the claims. Karen et al. teaches a lecithin-coated microcrystalline dantrolene composition suitable for intravenous injection. The dried composition may be reconstituted in water at 10-15% (wt/vol. Dantrolene) to form a stable suspension with particle size of 300-800 nm (sodium dantrolene) and 440±150 nm (dantrolene). See, particularly, page 797, the left column. The composition was used as intravenous injection in swines, rats, and dogs. See, particularly, pages 797-798. Karan et al. also teaches that the diameters of the microcrystals are vital as to the pulmonary hypertensive response. See, particularly, page 801, the left column.

6. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make a concentrated dantrolene sodium composition herein by method known in the art, such as incorporate the known pharmaceutical carrier, and/or excipients polyethylene glycol, dimethylacetamide, and/or benzalkonium chloride, either in solution, or in suspension.

A person of ordinary skill in the art would have been motivated to make a concentrated dantrolene sodium composition herein by method known in the art, such as incorporate the known pharmaceutical carrier, and/or excipients polyethylene glycol, dimethylacetamide, and/or benzalkonium chloride, either in solution, or in suspension because dantrolene sodium is known to be administered up to about 1000 mg per day (for patient with body weight of 75 kg) and make a high concentration composition is apparent for its convenience for administration. Further, concentration up to 50 mg/ml is known in the art. Further, method of making such concentrated composition is known in the art, as evidenced by the cited prior art, one of ordinary skill in the art would have been motivated to make such composition and enjoy a reasonable

expectation of success. The employment of the particular combination herein is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). Further, The optimization of a result effective parameter, e.g., particle size for an injectable composition, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. As to the dry powder, one of ordinary skill in the art would have been motivated to make a dry powder, which upon reconstitution would yield the solution or suspensions, because of the obvious convenience for storage. As to claims 103-105 which recite steps of simply combining the ingredients and mixing the combination, note such mixing step would have been within the purview of ordinary skilled artisan.

8. Claims 1, 3, 5-10, 12, 14, 18-26, 83-91, 93, 94, 96-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karan et al. (IDS) in view of Parikh et al. (US 5,922,355)

9. Karen et al. teaches a lecithin-coated microcrystalline dantrolene composition suitable for intravenous injection. The dried composition may be reconstituted in water at 10-15% (wt/vol. Dantrolene) to form a stable suspension with particle size of 300-800 nm (sodium dantrolene) and 440±150 nm (dantrolene). See, particularly, page 797, the left column. The composition was used as intravenous injection in swines, rats, and dogs. See, particularly, pages 797-798. Karan et al. also teaches that the diameters of the microcrystals is vital as to the pulmonary hypertensive response. See, particularly, page 801, the left column. As to safe for intravenous injection, it is noted that the specification defined the safe as:

10. [0015] "**Safe** for injection". We define "**safe** for injection" to mean a formulation that can be reliably injected intravenously into appropriate test subjects or model mammals, at relevant clinical doses, with a low incidence of life-threatening complications due to the formulation,

where low incidence means less than about 10% of cases, and preferably less than about 1% of cases. In particular, formulation-related toxicities, such as pulmonary emboli (PE) due to supermicron-sized particles or aggregates, pathologically altered arterial pressures, or severe vascular damage, must be limited to low incidence. See page 3.

11. It is note that Karan references discloses incident of pulmonary hypertensive response (page 801), however, it is no way a *life-threatening complication*. Therefore, the composition disclosed by Karan reference would meet the limitation of safe for intravenous rejection.

Karen et al. do not teach expressly the employment of a water-soluble surfactant.

However, Parikh et al. teaches a method of making submicronized particles by using additional surfactant with phospholipid. Such method produces particles have a volume weighted mean particle size at least one half smaller than obtainable using phospholipids alone. Composition so prepared is resistant to particle size growth on storage. See, particularly, the abstract. The suitable second surfactants including polyethylene glycols, polyethylene fatty acid ester, sorbitan fatty acid ester, polyvinyl alcohol, etc. See, particularly, col. 3, lines 6-32.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to further incorporate one or more of water-soluble surfactants, such as polyethylene glycol.

A person of ordinary skill in the art would have been motivated to further incorporate a water-soluble surfactant, such as polyethylene glycol because it will reduce the particle size and it is known that reducing particle size is beneficial for reducing the incident of pulmonary hypertensive response. The selection of a proper polyethylene glycol from commercial available products, such as PEG 300, PEG 400 etc, would have been within the purview of ordinary skill in the art. The employment of stabilizer in the composition for suspension would have been

obvious because stabilization of a pharmaceutical composition is beneficial. Further, Karen teaches that the second surfactant stabilized the particles size. The employment of the particularly polyethylene fatty acid, or sorbitan fatty acid ester would have been within the purview of one of ordinary skill in the art in view the teaching of polyethylene fatty acid ester, sorbitan fatty acid ester. The employment of that surfactant herein is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). The method of making the suspension, comprising simply admixture the dantrolene with liquid carrier would have been obvious as Karen et al. teach that the composition may be easily reconstituted. Finally, making a large unit dosage for a large animals would have been obvious as large animal need large dosage.

Response to the Arguments

Applicants' amendments and remarks and the declarations submitted December 12, 2008 have been fully considered, But are not persuasive with respect to the rejections set forth above.

12. The declaration under 37 CFR 1.132 filed December 12, 2008 by David M. Anderson is sufficient to overcome the rejection of claims 1, 3, 5-8, 10-12, 22, 95, 106, 107 and 110 based upon are JP 5320413.

13. The declarations under 37 CFR 1.132 filed December 12, 2008 are insufficient to overcome the rejection of claims 1, 3, 5-10, 12-14, 18-26, 83-91, 93, 94, 96-116 based upon Ellis et al. (IDS), in view of Patel et al. (6,294,192), Ramstack et al. (US 6,495,164), Bosch et al. (US 5,510,118), and Karen et al. (IDS) as set forth above, and the rejection of claims 1, 3, 5-10,

12-14, 18-26, 83-91, 93, 94, 96-116 based upon Karen et al. (IDS) as set forth above because of the following reasons:

14. As to Karan reference, Anderson's declaration asserted the composition disclosed in the reference is not "safe", as required in the claimed invention. However, there is no evidence either in the reference, or otherwise, showing that the composition will not meet the "safe" definition herein

15. [0015] "Safe for injection". We define "safe for injection" to mean a formulation that can be reliably injected intravenously into appropriate test subjects or model mammals, at relevant clinical doses, with a low incidence of life-threatening complications due to the formulation, where low incidence means less than about 10% of cases, and preferably less than about 1% of cases. In particular, formulation-related toxicities, such as pulmonary emboli (PE) due to supermicron-sized particles or aggregates, pathologically altered arterial pressures, or severe vascular damage, must be limited to low incidence. See page 3.

16. Particularly, the reference does not show any life-threatening complication in the animal model. It is noted that the 2-μ-filtered is much better than the commercial available product. Even the un-filtered is better than the commercial products. See table 2. Whether the composition disclosed by Karen reference is clinically safe is another issue. But it is certainly meet the "safe" definition herein (The application herein provides no evidence that the claimed products are any better than those disclosed by Karen et al.). Further, it would have been obvious to further optimize the condition so to reduce the particle size of the composition. See the obvious rejections based on Karen.

17. Further, the declarations refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP

§ 716. Particularly, the claims merely define the composition by requiring a water-soluble surfactant, plus all those desired functions. The declaration merely focuses on the particular examples with very specific surfactant(s), wherein the product is made with a particular procedure.

With respect to applicants' own data showing that Karan's composition is not safe, it is well settled patent law "that it is not a difficult matter to carry out a process in such a fashion that it will not be successful and, therefore, the failures of experimenters who have no interest in succeeding should not be accorded great weight" In re Michalek, 74 USPQ 108, at 109 citing Bullard Company et al v. Coe, 147 F.2d. 568, 64 USPQ 359." See, also MPEP 716.07.

With respect to the declaration of Dr. Benjamin G. Cameransi, Jr., it states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. First, the products of Karan et al. appear to meet the limitation of "safe" herein. Further, there is no evidence that at the time the claimed invention was make, one of ordinary skill in the art know of the teachings of the above cited references would still be unable to solve the problems, such as those mentioned by Dr. Muldoon.

Applicants assert that the particle size parameter is not a mere optimization of a parameter but is a critical, inventive aspect of the present invention. However, it is noted that the claims do not recite any limitation regarding the particle size. Further, since the cited references

teach or suggest each and every ingredient herein claimed, the optimization of the particle size would have been within the skill of ordinary artisan.

18. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shengjun Wang/
Primary Examiner, Art Unit 1617